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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
NATARAJAN, MEERA	
ART UNIT	**PAPER NUMBER**
1643	
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10/03/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/510,155	KELLY ET AL.	
	Examiner	Art Unit	
	Meera Natarajan	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 July 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above claim(s) *15-18 and 21-24* is/are withdrawn from consideration.

5)☒ Claim(s) *11 and 25* is/are allowed.

6)☒ Claim(s) *1-10,12-14,19 and 20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *05 October 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/23/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I, Claims 1-14, 19-20 and 25 and species election of SEQ ID NO:1 in the reply filed on 07/30/2007 is acknowledged. The traversal is on the ground(s) that Wolfe et al. does not teach a peptide that **"selectively"** binds to colon cancer cells. Applicant argues that Wolfe et al. teach that E. coli heat-stable enterotoxin (STa) which does bind primary and metastatic colorectal tumors has as its receptor Guanylyl cyclase C (GC-C) and Wolfe et al. discloses that GC-C is expressed not only by primary and metastatic colorectal tumors but also by adult intestinal epithelial cells. Therefore, Sta shows no preferential binding over non-cancerous intestinal epithelial cells. This is not found persuasive because although Wolfe et al. does state the Sta receptor GC-C is present in primary and metastatic colorectal tumors as well as in adult intestinal epithelial cells, Wolfe et al. goes on to further analyze that even though the STa receptor is present in normal cells, STa does not bind to adult intestinal epithelial cells. Wolfe et al. states the following: (see p. 397, right column last paragraph through p.398 left column)

> "In healthy adult humans, GC-C is expressed only by intestinal mucosal, not extraintestinal cells. Of significance, GC-C is expressed in brush border, but no basolateral membranes on the luminal side of tight junctions that form the impermeable intestinal epithelial cell barrier. Thus, GC-C is normally in an anatomically privileged location, sampling the luminal environment but denied access to the vascular compartment by epithelial tight junctions. Indeed, in comparison with inactive [STa], [Sta] did not accumulate differentially in the intestine of CD-1 nude mice in this study, supporting the suggestion that GC-C expressed by normal intestinal epithelial cells is isolated from the vascular compartment. To date, all human primary and metastatic colorectal tumors examined have expressed this marker, suggesting that GC-C is highly associated with the presence of colorectal cancer in extraintestinal sites. Thus

> GC-C on metastatic human colorectal cancer cells appears to be a highly specific target for receptor-based imagining agents, because GC-C expressed by normal intestinal epithelial cells is inaccessible to imaging agents in the circulation."

Wolfe et al. demonstrates that STa is highly selective for colon cancer cells when used *in vivo*. Therefore, the STa peptide taught by Wolfe et al. teaches the claimed peptide.

2. Claims 15-18, 21-24 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 07/30/2007.

3. After further consideration, the SEQ ID species election is withdrawn.

4. Claims 1-14, 19-20 and 25 will be examined on the merits.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-10, 12-14 and 19-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a composition comprising a peptide that selectively binds to HT29 colon cancer cells comprising arg-pro-met (RPM) sequence adjacent to the C-terminal cysteine as, does not reasonably provide enablement for a composition comprising just any peptide that selectively binds to just any colon cancer cell. The specification does not enable any person skilled in the art to

which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

7. In making a determination as to whether an application has met the requirements for enablement under 35 U.S.C. 112 ¶ 1, the courts have put forth a series of factors. See, In re Wands, 8 USPQ2d 1400, at 1404 (CAFC 1988); and Ex Parte Forman, 230 U.S.P.Q. 546 (BPAI 1986). The factors that may be considered include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While it is not essential that every factor be examined in detail, those factors deemed most relevant should be considered.

8. The claims are broadly drawn to a pharmaceutical composition comprising any cyclic peptide that selectively binds to any colon cancer cell. The peptide sequence formula disclosed in Claim 4 "A-X1-X2-X3-X4-X5-X6-X7-X8-X9-B, wherein X1-X9 are amino acid, wherein A and B are absent or are amino acids or peptides containing up to 6 amino acids, and wherein amino acids X2-X5 may be the same or different and each optionally may be absent" reads on hundreds of possible peptide sequences. Since Applicant has only provided working examples of a cyclic peptide (comprising SEQ ID NO:1) that contains the amino acid sequence "RPM" adjacent to the C-terminal cysteine (none of which are shown in Claim 9) is capable of selectively binding to HT29 colon cancer cells, undue experimentation would be required to support the enablement of all

cyclic peptide sequences that fit into the formulas of Claims 4, 5, and 6. Applicant discloses in the instant specification that "binding specificity was confirmed by showing that an RPM peptide successfully abolished binding of RPM-bearing phage to HT29 cells. In contrast, an unrelated peptide failed to block the RPM-phage binding. RPM was confirmed to be a functional consensus sequences by synthesizing alanine substitution mutations in the RPM sequence and determining their ability to compete for binding with wild-type RPM. Further, moving the RPM motif to the middle of the peptide abolished the ability of that peptide to compete with the wild type RPM peptide, suggesting that the cysteine plays a role in RPM binding to HT29 cells. (see specifications p.7 lines 10-13 and lines 21 through p. 8 line 3). Applicants own disclosure supports a **lack** of enablement of all the sequences listed in Claim 9 since none of them contain the "RPM" sequence.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

10. Claims 1-5, 12, 13 and 14 rejected under 35 U.S.C. 102(a) as being anticipated by Wolfe et al. (J. of Nuclear Medicine Vol. 43 No. 3 p.392-399, March 2002). The claims are drawn to a composition comprising a cyclic peptide that selectively binds to colon cancer cells wherein said peptide is conjugated to detectable radioactive label.

11. Wolfe et al. teach a cyclic peptide, E. Coli heath-stable enterotoxin (STa) that specifically binds (see arguments presented above under "Election/Restrictions") to colon cancer cells. Although the sequence of STa is not specifically taught, Wolfe et al. discloses STa is a 14 amino acid peptide. The 1st paragraph under the "Results" section on page 394 discloses an analog of STa wherein 6 cysteine residues were replaced by alanines confirming cysteines are present in the STa sequence. Claim 4 reads on a very broad scope of possible peptide sequences that can be as small as 2 amino acids to as long as 21 amino acids containing at least two cysteine residues. Wolfe et al. also teach a radiolabeled conjugate of STa to selectively target and image extraintestinal human colon cancer xenografts in vivo in nude mice. This compound was intravenously administered to nude mice bearing human colon cancer xenografts and specific targeting was evaluated by biodistribution and gamma camera imaging (see Figure 3). The references teach each and every limitation of the claims.

Claim Rejections - 35 USC § 103

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

14. Claims 1-5, 12-14, 19 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wolfe et al. (J. of Nuclear Medicine Vol. 43 No. 3 p.392-399, March 2002) in view of Mazar et al. (Patent #6277818).

15. The claims are drawn to a composition comprising a cyclic peptide that selectively binds to colon cancer cells wherein said peptide is conjugated to detectable radioactive label and/or a therapeutic agent, wherein said therapeutic agent is cytotoxic.

16. The teachings of Wolfe et al. are presented in the 102(b) rejection set forth above. Wolfe et al. does not teach conjugating STa to a therapeutic agent, this deficiency is made up for in Mazar et al.

17. Mazar et al. teach cyclic peptide ligands that target urokinase plasminogen activator receptor. The invention of Mazar et al. also comprises pharmaceutical compositions comprising said cyclic peptides linked to therapeutic moieties such as toxins (see column 1, paragraph 1, column 4 lines 1-28, and column 7 lines 57-64)

18. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to conjugate the cyclic peptide taught by Wolfe et al. to a therapeutic agent. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by teachings in Wolfe et al. and Mazar et al. because the conjugated therapeutic agent helps target the tumor cells and minimize nonspecific targeting and deliver the peptide and therapeutic agents to the tumor.

Conclusion

19. Claims 1-10, 12-14 and 19-20 are rejected.

20. Claims 11 and 25 are allowable.

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Meera Natarajan whose telephone number is 571-270-3058. The examiner can normally be reached on Monday-Thursday, 8:30AM-6:00PM, ALT. Friday. EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

LARRY R. HELMS, PH.D.
SUPERVISORY PATENT EXAMINER

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